Biomarker-Guided Versus Guideline-Based Treatment of Patients With Heart Failure Results From BIOSTAT-CHF

Ouwerkerk, Wouter; Zwinderman, Aeilko H.; Ng, Leong L.; Demissei, Biniyam; Hillege, Hans L.; Zannad, Faiez; van Veldhuisen, Dirk J.; Samani, Nilesh J.; Ponikowski, Piotr; Metra, Marco

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2017.11.041

Publication date:
2018

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 4, 2018

PUBLISHED BY ELSEVIER

Biomarker-Guided Versus Guideline-Based Treatment of Patients With Heart Failure

Results From BIOSTAT-CHF

Wouter Ouwerkerk, PhD,[a] Aeilko H. Zwinderman, PhD,[a] Leong L. Ng, MD, PhD,[b] Biniyam Demissei, MD, PhD,[c] Hans L. Hillege, MD, PhD,[c] Faiez Zannad, MD, PhD,[d] Dirk J. van Veldhuisen, MD, PhD,[c] Nilesh J. Samani, MD, PhD,[b] Piotr Ponikowski, MD, PhD,[e,f] Marco Metra, MD,[g] Jozine M. ter Maaten, MD, PhD,[c] Chim C. Lang, MD,[h] Pim van der Harst, MD, PhD,[c] Gerasimos Filippatos, MD, PhD,[i] Kenneth Dickstein, MD, PhD,[j,k] John G. Cleland, MD, PhD,[l] Stefan D. Anker, MD, PhD,[m] Adriaan A. Voors, MD, PhD[c]

ABSTRACT

BACKGROUND Heart failure guidelines recommend up-titration of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) to doses used in randomized clinical trials, but these recommended doses are often not reached. Up-titration may, however, not be necessary in all patients.

OBJECTIVES This study sought to establish the role of blood biomarkers to determine which patients should or should not be up-titrated.

METHODS Clinical outcomes of 2,516 patients with worsening heart failure from the BIOSTAT-CHF (BIOlogy Study to Tailored Treatment in Chronic Heart Failure) were compared between 3 theoretical treatment scenarios: scenario A, in which all patients are up-titrated to >50% of recommended doses; scenario B, in which patients are up-titrated according to a biomarker-based treatment selection model; and scenario C, in which no patient is up-titrated to >50% of recommended doses. The study conducted multivariable Cox regression using 161 biomarkers and their interaction with treatment, weighted for treatment-indication bias to estimate the expected number of deaths or heart failure hospitalizations at 24 months for all 3 scenarios.

RESULTS Estimated death or hospitalization rates in 1,802 patients with available (bio)markers were 16%, 16%, and 26%, respectively, in the ACE inhibitor/ARB up-titration scenarios A, B, and C. Similar rates for beta-blocker and MRA up-titration scenarios A, B, and C were 23%, 19%, and 24%, and 12%, 11%, and 24%, respectively. If up-titration was successful in all patients, an estimated 9.8, 1.3, and 12.3 events per 100 treated patients could be prevented at 24 months by ACE inhibitor/ARB, beta-blocker, and MRA therapy, respectively. Similar numbers were 9.9, 4.7, and 13.1 if up-titration treatment decision was based on a biomarker-based treatment selection model.

CONCLUSIONS Up-titrating patients with heart failure based on biomarker values might have resulted in fewer deaths or hospitalizations compared with a hypothetical scenario in which all patients were successfully up-titrated.
(J Am Coll Cardiol 2018;71:386–98) © 2018 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Clinical Epidemiology, Biostatistics & Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [b]Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, and NIHR Leicester Biomedical Research Centre, Glenfield Hospital, Leicester, United Kingdom; [c]Department of Cardiology, University of Groningen, Groningen, the Netherlands; [d]Inserm CIC 1433, Université de Lorraine, CHU de Nancy, Nancy, France; [e]Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [f]Cardiology Department, Military Hospital, Wroclaw, Poland; [g]Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; [h]School of Medicine Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom; [i]Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece; [j]Department of Cardiology, University of Stavanger, Stavanger, Norway; [k]Department of Clinical Science, University of Bergen, Bergen, Norway; [l]National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, United Kingdom; and the [m]Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Center, Göttingen, Göttingen, Germany.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2017.11.041

Major improvements in pharmaceutical and device heart failure treatment of heart failure have been achieved in the past year. Evidence from large randomized clinical trials demonstrates that angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid receptor antagonists (MRAs) improve clinical outcome in patients with mild-to-moderate heart failure (1–8). In large randomized clinical trials, treatment doses were up-titrated to pre-specified doses, which have become the guideline-recommended doses (9–12). Despite these improvements and recommendations, the prognosis of patients with heart failure remains poor (13–16), and in daily clinical practice the majority of patients do not achieve recommended doses (17–19). Although it is expected that most patients that achieve recommended doses will benefit from treatment, selected patients may not benefit from the recommended doses, but will experience side effects of ACE inhibitors and beta-blocker treatment. A personalized medicine approach in which patients who will not benefit from recommended ACE inhibitor/ARB and beta-blocker heart failure treatment might be selected by biomarkers, and might reduce the number of patients receiving treatment without benefit and improve overall outcome.

SEE PAGE 399

In this in silico study, we used data from the BIOSTAT-CHF (BIOlogy Study to Tailored Treatment in Chronic Heart Failure) project to identify such treatment selection markers. We hypothesized that biomarkers measured at baseline in serum or plasma of heart failure patients can identify whether patients benefit from recommended heart failure treatment or not. We developed models to estimate this benefit using 161 established and novel biomarkers, including standard biochemical blood parameters. We compared 3 theoretical treatment scenarios: scenario A, in which all patients are up-titrated to >50% of recommended doses according to the European Society of Cardiology guidelines (9–11); scenario B, in which patients are up-titrated by a biomarker-based treatment selection model; and scenario C, in which no patient is treated at >50% of recommended dose.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

BNP = B-type natriuretic peptide

BUN = blood urea nitrogen

CI = confidence interval

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

WAP-4C = WAP 4-disulfide core domain protein HE4

METHODS

PATIENTS. BIOSTAT-CHF is a multicenter prospective study of 2,516 patients from 69 centers in 11 European countries (20). Included patients were >18 years of age with symptoms of new onset or worsening heart failure, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels >400 pg/ml or >2,000 pg/ml, respectively. At inclusion, patients were treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion, and were not previously treated with evidence-based therapies (ACE inhibitor/ARB and beta-blocker) or were receiving ≤50% of the target doses of these drugs at the time of inclusion and had an anticipated initiation or up-titration of ACE inhibitor/ARB or beta-blocker therapy by the treating physician. Institutional Review Board approval was obtained in all countries.

EVIDENCE-BASED HEART FAILURE TREATMENT. Patients were treated according to evidence based European Society of Cardiology heart failure guidelines available at time of inclusion (9–11). These recommend up-titrating patients to recommended doses of ACE inhibitors/ARBs and beta-blockers, unless not tolerated or contraindicated (9–11). In BIOSTAT-CHF, suboptimally treated patients were included, and physicians were encouraged to

This work was supported by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010-020808-29). Dr. Metra has received consulting honoraria from Amgen, Bayer, Novartis, and Servier; and speaker fees from Abbott Vascular, Bayer, and ResMed. Dr. Lang has received consultancy fees and/or research grants from Amgen, AstraZeneca, MSD, Novartis, and Servier. Dr. van der Harst has received a research grant from Abbott. Dr. Filippatos has received fees and/or research grants from Novartis, Bayer, Cardiorentis, Vifor, Servier, Alere, and Abbott. Dr. Dickstein has received honoraria and/or research support from Medtronic, Boston Scientific, St. Jude Medical, Biotronik, Sorin, Merck, Novartis, Amgen, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, GlaxoSmithKline, Roche, Sanofi, Abbott, Otsuka, Leo, Servier, and Bristol-Myers Squibb. Dr. Cleland has received grant support from Amgen, Novartis, and Stealth Biopharmaceuticals; and honoraria from Servier. Dr. Anker has received grants from Vifor and Abbott Vascular; and consulting fees from Vifor, Bayer, Boehringer Ingelheim, Brahms, Cardiorentis, Janssen, Novartis, Relypsa, Servier, Stealth Peptides, and ZS Pharma. Dr. Voors has received consultancy fees and/or research grants from Alere, Amgen, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, GlaxoSmithKline, Merck/MSD, Novartis, Servier, Stealth Peptides, Singulex, Sphingotec, Trevena, Vifor, and ZS Pharma. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 24, 2017; revised manuscript received November 5, 2017, accepted November 7, 2017.

up-titrate patients to recommended treatment doses within 3 months after inclusion.

We recently published data from BIOSTAT-CHF showing that up-titrating patients to at least 50% of recommended ACE inhibitor/ARB and beta-blocker doses results in comparable survival or heart-failure-related hospitalization reduction compared with patients that reached ≥100% of recommended doses (21). We therefore considered patients successfully up-titrated when >50% of recommended dose was achieved after 3 months of up-titration. Inversely, we defined nonresponders as patients who did not achieve more that 50% recommended treatment dose. All analyses were separately performed for ACE inhibitors/ARBs and beta-blockers. In addition to ACE inhibitor/ARB and beta-blocker treatment, we also looked at MRA guideline-recommended treatment. Here we defined successful treatment as patients who achieved ≥50% of recommended treatment, and non-responding patient when <50% of recommended treatment dose was achieved. MRA treatment data was available at 9 months after inclusion.

DISEASE OUTCOME. Median follow-up of the BIOSTAT-CHF project was 21 months with an interquartile range of 15 to 27 months. Primary patient outcome in BIOSTAT-CHF was the first occurrence of all-cause mortality or heart failure-related hospitalization. Survival time was calculated from date of inclusion in BIOSTAT-CHF to date of death or heart failure hospitalization or date of censoring. Only patients who were at least followed for 3 months were included in the present analysis.

BIOMARKERS. A total of 161 biomarkers were considered as treatment selection markers. All markers were measured at inclusion of the patients. This included standard biochemical blood-parameters (hemoglobin, hematocrit, sodium, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, serum creatinine, blood urea nitrogen [BUN], bilirubin, serum iron, potassium), heart failure markers (LVEF, NT-proBNP, and BNP), 29 markers from the Luminex multiplexed bead-based immunoassay (Alere, San Diego, California) heart failure panel (22,23), and 92 peptide markers from a high-throughput technique using the Olink Proseek Multiplex Cardiovascular (CVD) III^{96x96} kit (Olink Proteomics, Uppsala, Sweden), which measures 92 selected inflammation-related proteins simultaneously in 1-μl plasma samples. The kit uses a proximity extension assay technology in which 92 oligonucleotide-labeled antibody probe pairs are allowed to bind to their respective target present in the sample.

The 92 peptides measured by Olink were normalized in arbitrary normalized protein expression units. Other biomarkers were normalized using Box-Cox transformations when deemed necessary. A complete list of all biomarkers and their summary statistics are shown in Online Table 1.

STATISTICAL ANALYSIS. Imputation of missing data. Patients in whom >50% or more biomarker values were missing were not included in the analyses. Remaining missing values were imputed using random forests regression models implemented in the mice package (24) of the R statistical program version 3.2.4 (R Project for Statistical Computing, Vienna, Austria). Five completed datasets were created.

Indication bias. Because BIOSTAT-CHF is not a randomized study, we adjusted for treatment indication bias. All analyses of the effect of successful up-titration treatment on mortality or hospitalization risk were inversely weighted with the probability of the given treatment. Given that treatment is defined here as a successful up-titration to >50% of European Society of Cardiology-recommended doses for ACE inhibitor/ARB or beta-blocker or not or ≥50% European Society of Cardiology-recommended MRA treatment dose. The probability of given treatment for a specific patient was modeled using a logistic regression model. All biomarkers were considered as predictor variables for successful up-titration. In addition, we considered 39 demographic and clinical predictor variables for prediction of the successful outcome of the up-titration (age, sex, race, body mass index, blood pressure, heart rate, smoking, alcohol use, heart failure etiology, heart failure duration, New York Heart Association functional class, and several heart failure symptoms and comorbid conditions). We used lasso penalization to obtain sparse logistic models consisting of a limited number of predictor variables. Optimal penalty parameters were obtained by 10-fold cross-validation. Analyses were performed for each imputed dataset and the calculated treatment probabilities were averaged per patient over the 5 imputed datasets. Performance of the logistic models was quantified using optimism-corrected C-statistics using 100 bootstrap samples, averaged over the imputed datasets.

Death or heart failure hospitalization and treatment-biomarker interaction. Mortality or heart failure hospitalization risk was modeled using the Cox regression model with given treatment as a stratum variable. Therefore, we did not assume proportional hazards for the effect of treatment on mortality or hospitalization risk. The assumed proportional hazards assumption of the biomarkers was

checked using Grambsch and Therneau's test implemented in the cox.zph function of the R statistical program (25).

We performed multivariable Cox regression with all 161 biomarkers. We used the split sample technique to obtain a training sample consisting of 80% of the patients in the original index cohort and the remaining 20% of the patients formed the test sample. The split-sample procedure was repeated 100 times. In all 100 training samples, we used lasso penalization to obtain sparse Cox regression models consisting of a limited number of the 161 biomarkers. Optimal penalty parameters were obtained by 10-fold cross-validation.

We performed separate analyses for patients who were successfully up-titrated to >50% of recommended treatment dose for either ACE inhibitors/ARBs or beta-blockers and for patients who were nonresponders as defined by lack of up-titration (≤50% of recommended treatment dose). This resulted in 6 different models predicting mortality or heart failure hospitalization; 3 models predicting mortality or heart failure hospitalization in successfully up-titrated patients for ACE inhibitors/ARBs, beta-blockers, and MRAs, and 3 for nonresponding patients who were up-titrated to ≤50% of recommended ACE inhibitor/ARB and beta-blocker doses and <50% recommended MRA dose. We stratified on given treatment and considered both the main effects of all biomarkers as well as all interactions of biomarkers with treatment. In the 100 test samples, we subsequently evaluated the goodness of fit of the selected sparse Cox regression models. We calculated both calibration and discrimination statistics (C-statistic and shrinkage statistic). Moreover, the benefit of successful and not successful up-titration was calculated for the patients in the test samples. All analyses were inversely weighted with the probability of the given treatment to account for indication bias.

Treatment benefit statistics. We calculated the expected number of events at 24 months follow-up for 3 scenarios: scenario A, if all patients are successfully up-titrated to >50% of recommended doses according to the European Society of Cardiology guidelines (≥50% for MRAs); scenario B, if all patients are up-titrated following a treatment strategy based on the biomarker values; and scenario C, if no patient is treated at >50% of recommended doses according to the European Society of Cardiology heart failure guidelines (≥50% for MRAs). We performed all analyses for ACE inhibitors/ARBs and beta-blockers separately. For scenario B, we decided to up-titrate when the probability of survival for mortality or hospitalization at 24 months for up-titrating was higher than for not up-titrating, and vice versa.

The survival probabilities were based on the difference of a patient's mean death or heart failure hospitalization probability at 24 months follow-up ($S(t = 24|...)$) under both treatments according to the sparse Cox regression models estimated for the associated training sample:

$$S(t = 24|\textit{successful up-titration}, X = x) - S(t = 24|\textit{unsuccessful up-titration}, X = x)$$

where X=x represents specific levels of the biomarkers selected in the Cox models for predicting mortality or heart failure hospitalization in the successfully and not successfully up-titrated patients, respectively. The difference was averaged over all test samples that included the specific patient, and was subsequently multiplied with total number of patients. This benefit statistic can be interpreted as the number of deaths or heart failure hospitalizations that is prevented at 24 months by successful up-titrating to >50% of recommended doses according to the European Society of Cardiology guidelines.

Benefit statistics were calculated for each test sample separately. The standard deviation of the benefit statistics over the 100 test samples was then used as an estimate of the standard error of the mean benefit statistic.

RESULTS

Of the 2,516 patients included in the index cohort, 151 patients died, 23 patients were censored before 3 months follow-up, and 242 patients had an LVEF >40%; these patients were excluded from the current data analysis. Of the remaining 2,100 patients, there were 298 patients with missing values on more than 50% of the biomarkers. Subsequent analyses were done with data from the remaining 1,802 patients. Because BIOSTAT-CHF is not a randomized trial, we corrected for the probability of being up-titrated to >50% of recommended treatment dose. Biomarkers predictive for up-titration and subsequent indication bias correction are presented in the Online Appendix. Of the 1,802 patients, 529 (29%) were up-titrated to >50% of recommended ACE inhibitor/ARB dose and 318 (18%) were up-titrated to >50% of recommended beta-blocker dose. We have MRA treatment data for 1,423 patients at 9 months after inclusion. Of these 1,423 patients, 14% (n = 195) were successfully up-titrated to ≥50% recommended treatment dose (2% [n = 28] to >50% recommended doses). Patient characteristics of patients achieving >50% recommended ACE inhibitor/ARB and beta-blocker dose and ≥50% recommended MRA dose and of those who did not respond to recommended treatment are presented in Table 1.

TABLE 1 Baseline Characteristics of the Patients Who Were Up-Titrated to >50% of Recommended ACE Inhibitor/ARB and Beta-Blocker and ≥50% MRA Dose and Those Who Were Not

	ACE Inhibitor/ARB			Beta-Blocker			MRA		
	Successful Up-Titration (n = 529)	No Successful Up-Titration (n = 1,273)	p Value	Successful Up-Titration (n = 318)	No Successful Up-Titration (n = 1,484)	p Value	Successful Up-Titration (n = 195)	No Successful Up-Titration (n = 1,228)	p Value
% of recommended ACE inhibitor/ ARB dose	100 ± 28	29 ± 18		61 ± 39	48 ± 38		54 ± 38	52 ± 39	
% of recommended beta-blocker dose	45 ± 32	34 ± 30		93 ± 18	25 ± 17		38 ± 30	37 ± 31	
Age, yrs	66.36 ± 11.85	68.15 ± 12.12	0.004	66.14 ± 12.63	67.94 ± 11.92	0.02	63.21 ± 12.35	67.71 ± 11.89	<0.00001
Male	395 (75)	967 (76)	0.56	235 (74)	1,127 (76)	0.44	161 (83)	914 (74)	0.01
Caucasian	523 (99)	1,259 (99)	0.29	314 (99)	1,468 (99)	0.04	187 (96)	1,219 (99)	0.0006
BMI, kg/m^2	28.93 ± 6.02	27.49 ± 5.26	<0.00001	28.41 ± 5.57	27.81 ± 5.51	0.09	28.84 ± 5.55	27.87 ± 5.51	0.02
Systolic blood pressure, mm Hg	130.04 ± 22.37	121.24 ± 20.50	<0.00001	125.47 ± 21.70	123.46 ± 21.37	0.13	121.62 ± 18.39	125.68 ± 21.24	0.006
Diastolic blood pressure, mm Hg	79.03 ± 13.71	73.68 ± 12.60	<0.00001	78.35 ± 14.45	74.58 ± 12.77	0.00002	75.03 ± 11.24	76.36 ± 13.35	0.14
Heart rate, beats/min	79.88 ± 20.33	79.97 ± 19.19	0.93	85.30 ± 22.25	78.80 ± 18.70	<0.00001	80.66 ± 18.97	79.87 ± 20.29	0.59
Smoking (current/ever/ never)	197/256/76	450/630/193	0.73	101/177/40	546/709/229	0.04	63/94/38	450/602/176	0.14
Alcohol use	368 (70)	909 (71)	0.45	203 (64)	1,074 (72)	0.003	132 (68)	872 (71)	0.33
Ischemic HF etiology	261 (49)	563 (44)	0.05	163 (51)	661 (45)	0.03	100 (51)	584 (48)	0.33
HF duration, yrs	8.81 (4.43–14.09)	7.59 (3.34–13.20)	0.50	8.54 (3.77–17.02)	7.64 (3.49–12.72)	0.39	10.52 (5.86–15.42)	6.76 (2.89–12.93)	0.27
NYHA functional class III/IV	244 (46)	509 (40)	0.02	134 (42)	619 (42)	0.89	83 (43)	566 (46)	0.36
LVEF	29 (24–34)	28 (22–34)	0.0005	29 (24–34)	29 (24–34)	0.3	24 (19–29)	29 (24–34)	0.00001
NT-proBNP, ng/l	32,109 (29,824–34,465)	33,454 (30,868–35,940)	0.00001	32,593 (30,378–35,101)	32,919 (30,630–35,676)	0.19	32,008 (29,504–34,411)	32,704 (30,398–35,513)	0.03
Edema	228 (43)	603 (47)	0.10	156 (49)	675 (45)	0.25	86 (44)	526 (43)	0.74
Orthopnea	150 (28)	431 (34)	0.02	82 (26)	499 (34)	0.006	62 (32)	366 (30)	0.58
Rales >1/3 up lung fields	44 (19)	125 (19)	0.98	17 (12)	152 (20)	0.03	12 (13)	104 (18)	0.21
Jugular venous pressure	111 (29)	281 (31)	0.45	63 (28)	329 (31)	0.37	43 (30)	240 (27)	0.43
Hepatomegaly	60 (11)	184 (14)	0.07	39 (12)	205 (14)	0.45	39 (20)	125 (10)	0.00007
Hypertension	349 (66)	731 (57)	0.0007	195 (61)	885 (60)	0.58	107 (55)	750 (61)	0.10
Atrial fibrillation	209 (40)	564 (44)	0.06	163 (51)	610 (41)	0.0009	80 (41)	518 (42)	0.76
Myocardial infarction	188 (36)	491 (39)	0.23	113 (36)	566 (38)	0.38	61 (31)	441 (36)	0.21
PCI	106 (20)	285 (22)	0.27	72 (23)	319 (21)	0.65	39 (20)	260 (21)	0.71
CABG	70 (13)	220 (17)	0.03	47 (15)	243 (16)	0.48	23 (12)	183 (15)	0.25
None	427 (24)	932 (52)	0.02	234 (13)	1,125 (62)	0.52	136 (10)	969 (68)	0.004
Pacemaker only	28 (2)	89 (5)		16 (1)	101 (6)		8 (1)	80 (6)	
ICD only	31 (2)	121 (7)		30 (2)	122 (7)		25 (2)	84 (6)	
CRT only	11 (1)	24 (1)		7 (0)	28 (2)		5 (0)	19 (1)	
ICD and CRT	31 (2)	102 (6)		30 (2)	103 (6)		20 (1)	72 (5)	
Other	1 (0)	5 (0)		1 (0)	5 (0)		1 (0)	4 (0)	
Diabetes mellitus	182 (34)	389 (31)	0.11	97 (31)	474 (32)	0.62	63 (32)	351 (29)	0.29
COPD	70 (13)	220 (17)	0.03	42 (13)	248 (17)	0.12	28 (14)	185 (15)	0.80
Stroke	40 (8)	122 (10)	0.17	20 (6)	142 (10)	0.06	12 (6)	112 (9)	0.17
Peripheral artery disease	46 (9)	142 (11)	0.12	27 (8)	161 (11)	0.21	16 (8)	121 (10)	0.47
Aldosterone antagonists	267 (50)	719 (56)	0.02	150 (47)	836 (56)	0.003	156 (80)	621 (51)	<0.00001
Loop diuretics	526 (99)	1,268 (100)	0.61	317 (100)	1,477 (100)	0.7	194 (99)	1,221 (99)	0.92
Digoxin	82 (16)	242 (19)	0.08	54 (17)	270 (18)	0.61	50 (26)	206 (17)	0.003
Hemoglobin, g/dl	12.69 ± 1.73	12.00 ± 2.00	<0.00001	12.52 ± 1.81	12.00 ± 2.00	0.13	12.71 ± 1.79	13.00 ± 2.00	0.14
Creatinine, µmol/l	481 (470–500)	491 (470–515)	<0.00001	484 (467–506)	487 (467–510)	0.19	482 (463–497)	484 (463–508)	0.09
BUN, mmol/l	25.5 (24.2–31.6)	29.0 (24.0–35.0)	<0.00001	26.7 (23.5–32.4)	28.0 (23.0–34.0)	0.005	28.0 (22.7–32.5)	27.0 (23.0–33.0)	0.69

Continued on the next page

TABLE 1 Continued

	ACE Inhibitor/ARB			Beta-Blocker			MRA		
	Successful Up-Titration (n = 529)	No Successful Up-Titration (n = 1,273)	p Value	Successful Up-Titration (n = 318)	No Successful Up-Titration (n = 1,484)	p Value	Successful Up-Titration (n = 195)	No Successful Up-Titration (n = 1,228)	p Value
eGFR MDRD formula, ml/min/1.73 m^2	71 ± 22	64 ± 24	<0.00001	68 ± 24	65 ± 23	0.09	73 ± 20	67 ± 23	0.001
Sodium, mmol/l	138.85 ± 3.55	138.06 ± 3.81	0.00004	138.62 ± 3.46	138.22 ± 3.81	0.07	138.56 ± 3.84	138.53 ± 3.60	0.91
Potassium, mmol/l	3.24 ± 0.53	3.29 ± 0.56	0.07	3.24 ± 0.51	3.28 ± 0.56	0.20	3.19 ± 0.50	3.28 ± 0.56	0.01
BNP, pg/ml	3,931 (3,624–4,227)	4,010 (3,624–4,438)	0.04	3,966 (3,496–4,482)	3,984 (3,496–4,343)	0.92	3,991 (3,418–4,172)	3,937 (3,418–4,319)	0.84

Values are n, mean ± SD, n (%), or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

MULTIVARIABLE TREATMENT SELECTION MARKERS. To distinguish patients who benefited from up-titration from those who did not, we created 2 models. From 161 biomarkers, we first identified the strongest biomarkers to predict clinical events (death of heart failure hospitalization) despite successful up-titration with either ACE inhibitors/ARBs or beta-blockers. Most frequently selected biomarkers are reported in Online Table 2. BUN, fibroblast growth factor 23, and pro-enkephalin were the strongest predictors of clinical events in patients that were successfully up-titrated with ACE inhibitors/ARBs. Serum creatinine, galectin-3, ST2, and albumin were the strongest predictors of clinical events in patients that were successfully up-titrated with beta-blockers (Online Table 3). Predictive biomarkers for events in up-titrated patients with MRAs are presented in Online Table 4.

In the second model, we identified the strongest biomarkers to predict clinical events in patients who were NOT successfully up-titrated with either ACE inhibitors/ARBs or beta-blockers. Fibroblast growth factor 23, BUN, cystatin C, ST2, WAP 4-disulfide core domain protein HE4 (WAP-4C), and insulin-like growth factor binding protein 2 were the strongest predictors of clinical events in patients that were not successfully up-titrated with ACE inhibitors/ARBs. Fibroblast growth factor 23, cystatin C, BUN, WAP-4C, and NT-proBNP were the strongest predictors of clinical events in patients that were not successfully up-titrated with beta-blockers.

The treatment selection models had reasonable performances for the patients in the test sets. Averaged C-statistics for ACE inhibitor/ARB models were 0.74 (95% confidence interval [CI]: 0.68 to 0.80) in up-titrated patients, and 0.77 (95% CI: 0.70 to 0.83) in non-up-titrated patients, respectively. Beta-blocker treatment selection models averaged C-statistics were 0.75 (95% CI: 0.70 to 0.82) in up-titrated patients, and 0.78 (95% CI: 0.73 to 0.83) in non-up-titrated patients, respectively. C-statistics for MRA treatment selection models were 0.65 (95% CI: 0.56 to 0.74) and 0.77 (95% CI: 0.71 to 0.86) in up-titrated and non-up-titrated patients.

Using both models, we were able to calculate survival probability at 24 months for both scenarios (successful or nonsuccessful up-titration). The scenario with the highest probability was considered the most beneficial one for the individual patient. In 2% (n = 42) of patients, the highest probability was found in patients who were not successfully up-titrated with ACE inhibitors/ARBs. Characteristics of these patients are presented in **Table 2**. Patients not benefitting from ACE inhibitor/ARB up-titration were younger, more frequently smokers, with less atrial fibrillation and higher hemoglobin and BUN, but lower heart rate and NT-proBNP levels. In 33% (n = 592) of patients, the highest survival probability was found in patients who were not successfully up-titrated with beta-blockers. Characteristics of these patients are presented in **Table 2**. Patients not benefitting from beta-blocker up-titration were older, leaner, and more frequently smokers or former smokers. They also had less ischemic heart failure, but more myocardial infarction, and other comorbidities. They also had significantly higher LVEF, NT-proBNP, BUN, and creatinine levels, and lower diastolic blood pressure, heart rate, hemoglobin, and estimated glomerular filtration rate levels. Up-titrating MRA treatment was not beneficial for 13% (n = 184) of the patients.

CLINICAL EVENTS ACCORDING TO THE 3 HYPOTHETICAL SCENARIOS. Kaplan-Meier curves for ACE inhibitor/ARB scenarios are presented

TABLE 2 Characteristics of Patients Who Did Benefit From ACE Inhibitor/ARB, Beta-Blocker, or MRA Up-Titration and Those Who Did Not

	ACE Inhibitor/ARB			Beta-Blocker			MRA		
	Benefit Up-Titration (n = 1,760)	No Benefit Up-Titration (n = 42)	p Value	Benefit Up-Titration (n = 1,210)	No Benefit Up-Titration (n = 592)	p Value	Benefit Up-Titration (n = 1,573)	No Benefit Up-Titration (n = 229)	p Value
% of recommended ACE inhibitor/ ARB dose	50 ± 39	57 ± 41		51 ± 38	47 ± 40		49 ± 39	59 ± 39	
% of recommended beta-blocker dose	37 ± 31	41 ± 32		37 ± 31	36 ± 32		37 ± 32	37 ± 28	
Age, yrs	67.72 ± 12.00	63.37 ± 14.00	0.05	65.93 ± 12.13	71.08 ± 11.18	<0.00001	68.04 ± 12.04	64.77 ± 11.88	0.0001
Male	1,331 (76)	31 (74)	0.79	922 (76)	440 (74)	0.38	1,219 (77)	143 (62)	<0.00001
Caucasian	1,742 (99)	40 (95)	0.08	1,194 (99)	588 (99)	0.54	1,555 (99)	227 (99)	0.42
BMI, kg/m^2	27.89 ± 5.55	28.82 ± 4.22	0.18	28.37 ± 5.72	26.99 ± 4.98	<0.00001	27.86 ± 5.55	28.27 ± 5.39	0.30
Systolic blood pressure, mm Hg	123.67 ± 21.46	129.81 ± 19.94	0.06	124.26 ± 21.77	122.9 ± 20.73	0.20	123.26 ± 21.44	127.61 ± 21.09	0.004
Diastolic blood pressure, mm Hg	75.18 ± 13.15	78.07 ± 13.62	0.18	76.23 ± 13.53	73.23 ± 12.13	<0.00001	74.87 ± 13.11	77.80 ± 13.26	0.002
Heart rate, beats/min	80.05 ± 19.63	75.24 ± 13.49	0.03	80.91 ± 19.36	77.97 ± 19.72	0.003	80.62 ± 19.68	75.29 ± 17.72	0.00004
Smoking (current/ever/ never)	626/866/268	21/20/1	0.03	417/584/209	230/302/60	0.0003	560/779/234	87/107/35	0.72
Alcohol use	1,246 (71)	31 (74)	0.68	857 (71)	420 (71)	0.94	1,094 (70)	183 (80)	0.0009
Ischemic HF etiology	801 (46)	23 (55)	0.23	582 (48)	242 (41)	0.004	715 (45)	109 (48)	0.54
HF duration, yrs	8.02 (3.55-13.4)	3.54 (1.60-6.59)	0.20	8.34 (3.78-13.54)	6.38 (2.61-12.46)	0.31	8.30 (3.27-13.74)	5.80 (5.03-8.84)	0.28
NYHA functional class III/IV	731 (42)	22 (52)	0.16	498 (41)	255 (43)	0.44	618 (39)	135 (59)	<0.00001
LVEF	29 (24-34)	29 (24-34)	0.19	27 (23-34)	29 (24-34)	0.00001	28 (23-34)	29 (24-36)	<0.00001
NT-proBNP, ng/l	32,900 (30,630-35,620)	27,928 (26,980-32,965)	0.01	32,635 (30,247-35,086)	33,593 (31,140-36,655)	0.00003	33,143 (30,708-35,788)	31,303 (29,506-33,500)	0.00001
Edema	818 (46)	13 (31)	0.05	558 (46)	273 (46)	1.00	753 (48)	78 (34)	0.00009
Orthopnea	567 (32)	14 (33)	0.88	404 (33)	177 (30)	0.14	538 (34)	43 (19)	<0.00001
Rales >1/3 up lung fields	166 (19)	3 (14)	0.58	108 (18)	61 (20)	0.43	159 (20)	10 (12)	0.10
Jugular venous pressure	387 (31)	5 (16)	0.07	256 (30)	136 (31)	0.80	365 (32)	27 (16)	0.00001
Hepatomegaly	240 (14)	4 (10)	0.44	166 (14)	78 (13)	0.75	224 (14)	20 (9)	0.02
Hypertension	1,052 (60)	28 (67)	0.37	713 (59)	367 (62)	0.21	940 (60)	140 (61)	0.69
Atrial fibrillation	763 (43)	10 (24)	0.01	517 (43)	256 (43)	0.84	716 (46)	57 (25)	<0.00001
Myocardial infarction	668 (38)	11 (26)	0.12	415 (34)	264 (45)	0.00002	595 (38)	84 (37)	0.74
PCI	385 (22)	6 (14)	0.24	248 (20)	143 (24)	0.08	345 (22)	46 (20)	0.53
CABG	282 (16)	8 (19)	0.60	180 (15)	110 (19)	0.04	254 (16)	36 (16)	0.87
None	1,326 (74)	33 (2)	0.31	927 (51)	432 (24)	0.39	1,177 (65)	182 (10)	0.37
Pacemaker only	116 (6)	1 (0)		70 (4)	47 (3)		105 (6)	12 (1)	
ICD only	151 (8)	1 (0)		101 (6)	51 (3)		133 (7)	19 (1)	
CRT only	34 (2)	1 (0)		25 (1)	10 (1)		34 (2)	1 (0)	
ICD and CRT	127 (7)	6 (0)		83 (5)	50 (3)		118 (7)	15 (1)	
Other	6 (0)	0 (0)		4 (0)	2 (0)		6 (0)	0 (0)	
Diabetes mellitus	560 (32)	11 (26)	0.44	367 (30)	204 (34)	0.08	506 (32)	65 (28)	0.25
COPD	287 (16)	3 (7)	0.11	194 (16)	96 (16)	0.92	259 (16)	31 (14)	0.26
Stroke	162 (9)	0 (0)	0.04	101 (8)	61 (10)	0.17	148 (9)	14 (6)	0.1
Peripheral artery disease	185 (11)	3 (7)	0.48	120 (10)	68 (11)	0.31	173 (11)	15 (7)	0.04
Aldosterone antagonists	966 (55)	20 (48)	0.35	692 (57)	294 (50)	0.003	854 (54)	132 (58)	0.34
Loop diuretics	1,752 (100)	42 (100)	0.66	1,203 (99)	591 (100)	0.22	1,567 (100)	227 (99)	0.3
Digoxin	321 (18)	3 (7)	0.06	231 (19)	93 (16)	0.08	296 (19)	28 (12)	0.02
Hemoglobin, g/dl	12.36 ± 1.85	13.00 ± 1.00	0.004	12.79 ± 1.73	12.00 ± 2.00	<0.00001	12.40 ± 1.87	12.23 ± 1.68	0.17
Creatinine, µmol/l	486 (461-510)	488 (461-508)	0.55	482 (476-502)	500 (476-527)	<0.00001	489 (451-514)	472 (451-491)	<0.00001
BUN, mmol/l	28.0 (26.9-33.6)	33.0 (27.0-36.0)	0.002	27.4 (24.4-32.8)	29.0 (24.0-35.0)	0.0001	28.4 (21.5-34)	25.2 (21.5-30.5)	<0.00001
eGFR MDRD formula, ml/min/1.73 m^2	66.00 ± 23.00	70.00 ± 25.00	0.29	70.00 ± 22.00	56.00 ± 23.00	<0.00001	64.00 ± 23.00	78.16 ± 21.68	<0.00001
Sodium, mmol/l	138.28 ± 3.75	138.95 ± 3.88	0.27	138.42 ± 3.64	138.03 ± 3.97	0.04	138.11 ± 3.84	139.58 ± 2.79	<0.00001

Continued on the next page

TABLE 2 Continued

	ACE Inhibitor/ARB			Beta-Blocker			MRA		
	Benefit Up-Titration (n = 1,760)	No Benefit Up-Titration (n = 42)	p Value	Benefit Up-Titration (n = 1,210)	No Benefit Up-Titration (n = 592)	p Value	Benefit Up-Titration (n = 1,573)	No Benefit Up-Titration (n = 229)	p Value
Potassium, mmol/l	3.27 ± 0.55	3.29 ± 0.53	0.86	3.26 ± 0.53	3.31 ± 0.58	0.08	3.27 ± 0.55	3.33 ± 0.52	0.10
BNP, pg/ml	3,985 (2,090–4,357)	3,124 (2,090–3,823)	0.04	3,914 (3,744–4,282)	4,182 (3,744–4,457)	0.008	3,999 (2,631–4,394)	3,403 (2,631–3,877)	0.004

Values are n, mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

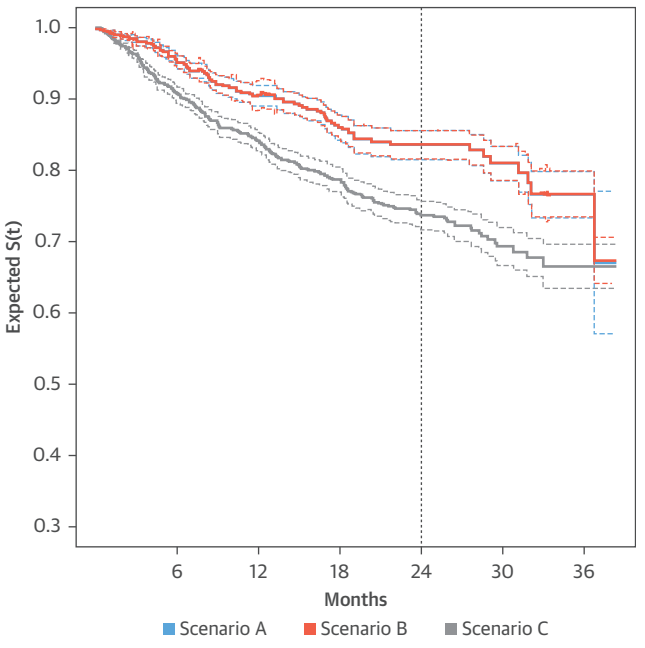
in Figure 1. Mortality or heart failure hospitalization was highest in the scenario in which no patient was up-titrated to ≥50% of the recommended dose. Patients who were up-titrated based on their biomarker profile had the lowest risk of death or heart failure hospitalization.

Estimated event rate and averaged expected events at 24 months for each of the 3 hypothetical scenarios are presented in Table 3. If all patients were successfully up-titrated to >50% of recommended doses ACE inhibitors/ARBs (scenario A), estimated death or hospital admission occurred in 297 (95% CI: 260 to 335) patients. If patients were up-titrated with ACE inhibitors/ARBs following a treatment strategy based on the biomarker values (scenario B), estimated death or hospital admission occurred in 296 (95% CI: 260 to 333) patients. If no patient was treated with >50% of recommended doses of ACE inhibitors/ARBs (scenario C), estimated death or hospital admission occurred in 474 (95% CI: 438 to 511) patients. Up-titrating ACE inhibitors/ARBs to >50% of recommended dose compared with ≤50% recommended dose resulted in 174 fewer events (95% CI: 128 to 227; p = 0.0003). Per 100 treated patients, this means that 9.8 (95% CI: 7.1 to 12.6) fewer events were seen in this scenario. The biomarkers-based approach led to 178 fewer events (95% CI: 130 to 226; p = 0.0003) compared with the ≤50% recommended dose group. Per 100 treated patients this resulted in 9.9 (95% CI: 7.2 to 12.6) fewer events.

Kaplan-Meier curves for beta-blocker scenarios are presented in Figure 2. Mortality or heart failure hospitalization was highest in the scenario where no patient was up-titrated to ≥50% of the recommended dose. Patients who were up-titrated based on their biomarker profile had the lowest risk of death or heart failure hospitalization, which was slightly lower compared with a scenario in which all patients were up-titrated to >50% of the recommended dose of ACE inhibitors/ARBs.

Estimated event rate and averaged expected events at 24 months for each of the 3 hypothetical scenarios are presented in Table 3. If all patients were successfully up-titrated to recommended beta-blocker doses (scenario A), estimated death or hospital admission occurred in 404 (95% CI: 332 to 477) patients. If patients were up-titrated with beta-blockers following a treatment strategy based on the biomarker values (Scenario B), estimated death or hospital admission occurred in 345 (95% CI: 300 to 389) patients. If no patient was treated with

FIGURE 1 Estimated Kaplan-Meier Survival Curves Based on 3 Scenarios for Up-Titrating ACE Inhibitors/ARBs



Estimated Kaplan-Meier survival curves with the expected event-free survival rate and time in months based on 3 scenarios **(blue, orange, and gray lines)**: scenario A, if all patients were up-titrated to >50% of recommended angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) dose **(blue)**; scenario B, if all patients were up-titrated according to biomarker-selection model **(orange)**; and scenario C, if no patient was up-titrated to >50% of recommended ACE inhibitor/ARB dose **(gray)**, with 95% confidence interval **(dashed lines)**.

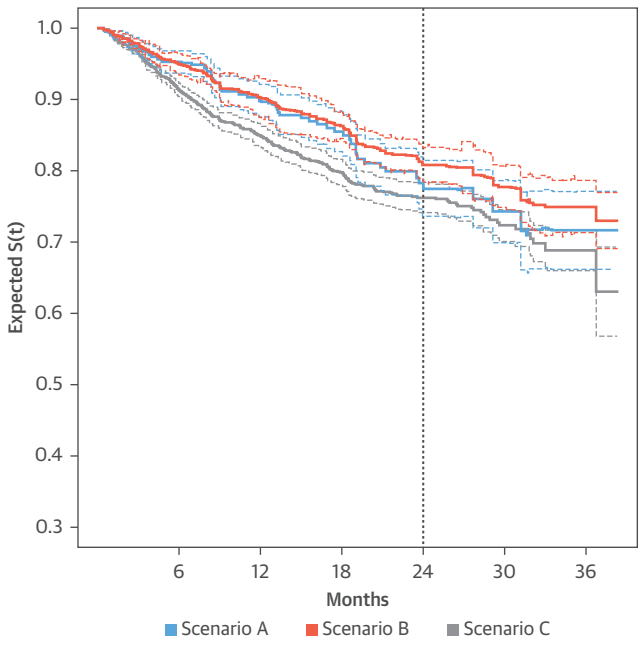
TABLE 3 Estimation of Mortality or Heart Failure Hospitalizations at 24 Months

	Scenario A	Scenario B	Scenario C
ACE inhibitor/ARB			
Estimated event rate at 24 months	16	16	26
Estimated number of events	297 (260 to 335)	296 (260 to 333)	474 (438 to 511)
Estimated event reduction compared with scenario C	177 (128 to 227)	178 (130 to 226)	–
Estimated event reduction compared with scenario C per 100 treated patients	9.8 (7.1 to 12.6)	9.9 (7.2 to 12.6)	–
Beta-blocker			
Estimated event rate at 24 months	23	19	24
Estimated number of events	404 (332 to 477)	345 (300 to 389)	428 (391 to 466)
Estimated event reduction compared with scenario C	24 (–54 to 103)	84 (40 to 128)	–
Estimated event reduction compared with scenario C per 100 treated patients	1.3 (–3.0 to 5.7)	4.7 (2.2 to 7.1)	–
MRA			
Estimated event rate at 24 months	12	11	24
Estimated number of events	215 (150 to 280)	201 (147 to 255)	437 (405 to 469)
Estimated event reduction compared with scenario C	222 (147 to 298)	236 (170 to 303)	–
Estimated event reduction compared with scenario C, per 100 treated patients	12.3 (8.1 to 16.5)	13.1 (9.4 to 16.8)	–

Values are % or n (95% confidence interval). Scenario A was if all patients were successfully up-titrated to >50% of recommended dose, scenario B was if up-titration was based on the biomarker treatment selection model, and scenario C was if no patient was successfully up-titrated for ACE inhibitors/ARBs.

Abbreviations as in Table 1.

FIGURE 2 Estimated Kaplan-Meier Survival Curves Based on 3 Scenarios for Up-Titrating Beta-Blockers



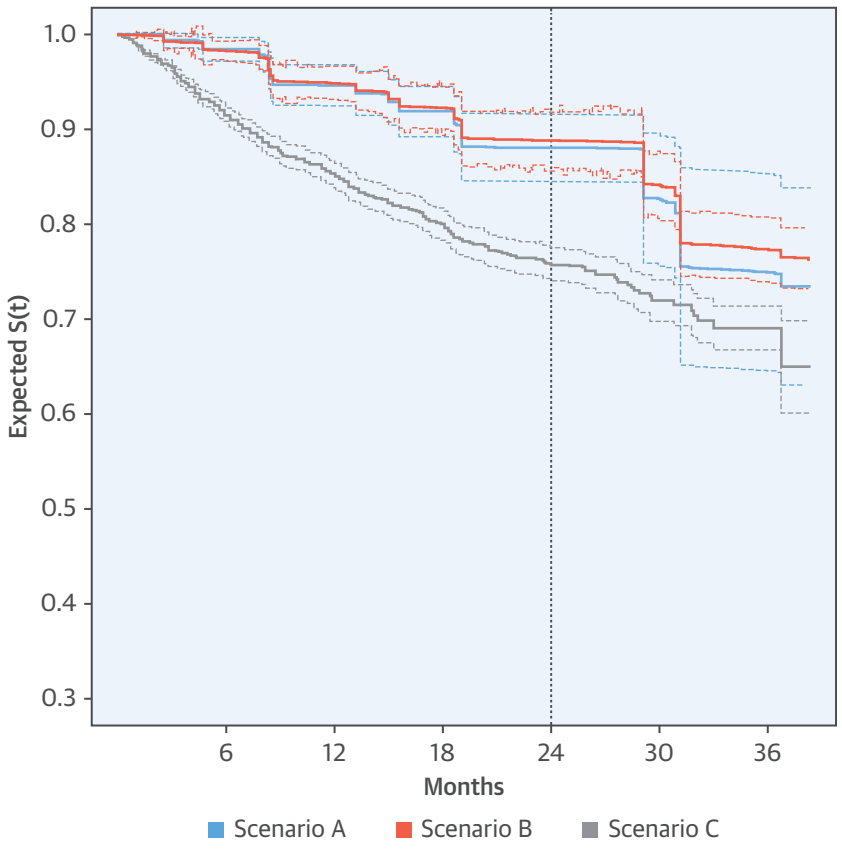
Estimated Kaplan-Meier survival curves with the expected event-free survival rate and time in months based on 3 scenarios **(blue, orange, and gray lines)**: scenario A, if all patients were up-titrated to >50% of recommended beta-blocker dose **(blue)**; scenario B, if all patients were up-titrated according to biomarker-selection model **(orange)**; and scenario C, if no patient was up-titrated to >50% of recommended of beta-blocker dose **(gray)**, with 95% confidence interval **(dashed lines)**.

recommended doses of beta-blockers (Scenario C), estimated death or hospital admission occurred in 428 (95% CI: 391 to 466) patients. Up-titrating beta-blockers to >50% of recommended dose compared with ≤50% resulted in 24 fewer events (95% CI: −54 to 103; p = 0.50). The biomarkers-based approach led to 84 fewer events (95% CI: 40 to 128; p = 0.01) compared with the ≤50% recommended dose group. This means that 1.3 (95% CI: −3.0 to 5.7) and 4.7 (95% CI: 2.2 to 7.1) events could be prevented per 100 treated patients in both scenarios.

When considering up-titrating to both 50% of recommended ACE inhibitor/ARB and beta-blocker dose we estimated that 222 (95% CI: 147 to 298) events could be prevented when all patients were up-titrated to at least 50% recommended treatment dose for both ACE inhibitors/ARBs and beta-blockers. Another 14 (95% CI: −52 to 80) events could be prevented when the decision to up-titrated was based on a biomarker-based model (Online Appendix).

For MRA treatment we estimated that not up-titrating patients to ≥50% of recommended MRA dose would result in 437 (95% CI: 405 to 469) events. When we would up-titrate all patients, this would be reduced with 222 (95% CI: 147 to 298; p = 0.0001) events to 215 (95% CI: 150 to 280). Our biomarker-based model resulted in 236 (95% CI: 170 to 303; p = 0.0004) less events than when no patient would be up-titrated to ≥50% of recommended MRA dose.

CENTRAL ILLUSTRATION **Biomarker-Guided Treatment in Heart Failure: Estimated Kaplan-Meier Survival Curves Based on 3 Scenarios for Up-Titrating MRAs**



Ouwerkerk, W. et al. J Am Coll Cardiol. 2018;71(4):386–98.

Estimated Kaplan-Meier survival curves with the expected event-free survival rate and time in months based on 3 scenarios **(blue, orange, and gray lines)**: scenario A, if all patients were up-titrated to ≥50% of recommended mineralocorticoid receptor antagonist (MRA) dose **(blue)**; scenario B, if all patients were up-titrated according to biomarker-selection model **(orange)**; and scenario C, if no patient was up-titrated to ≥50% of recommended of MRA dose **(gray)**, with 95% confidence interval **(dashed lines)**.

DISCUSSION

We hypothesized that not every patient with heart failure with reduced ejection fraction will benefit from maximal up-titration with either ACE inhibitors/ARBs or beta-blockers. We therefore tested 3 hypothetical scenarios: scenario A, in which all patients were up-titrated to >50% of recommended ACE inhibitor/ARB or beta-blocker dose; scenario B, in which all patients were up-titrated or not based on a biomarker model; and scenario C, in which no patient was up-titrated to >50% of recommended ACE inhibitor/ARB or beta-blocker dose (**Central Illustration**). Our models estimated that the highest number of events would have occurred in scenario C and the lowest number of events in scenario B. The present results from this novel approach suggest that some patients do not benefit from maximally recommended doses.

There are many biomarkers known to influence therapeutic response and survival (26,27), and there have been many attempts to use biomarker levels for evaluating treatment response and outcome (28). However, no models were developed using a multitude of biomarkers to estimate and compare the risk of mortality or heart failure hospitalization in up-titrated and non-up-titrated patients.

We recently published a meta-analysis on all prognostic heart failure models and an average C-statistics for predicting mortality or heart failure-related hospitalization of 0.68 (29). Thus, the biomarker-based treatment selection models in the

present paper have similar predictive performance compared with existing models. Most of these prognostic models were based on clinical and biographical patient characteristics with few biomarkers. The association of some biomarkers that we identified (e.g., NT-proBNP, BUN, ST2, hemoglobin) with mortality or heart failure hospitalization risk in heart failure patients is well known (9,10,30–37), but a differential predictive value in patients who were successfully up-titrated versus those who were not is as yet unknown. This observation may be useful to identify residual heart failure disease and additional treatment targets in heart failure patients. Although our biomarker-based treatment selection models have comparable performance to other prediction models, the performance of these models is still modest and they have large confidence bounds. In this study, we only looked at benefit, and did not take harm into account. Not up-titrating might be more beneficial for a patient; however, up-titrating might not do harm.

We decided to dichotomize up-titration into successful or not successful. In clinical practice, the actual doses of ACE inhibitors/ARBs and beta-blockers vary substantially. As we recently published data from BIOSTAT-CHF showing that up-titrating patients to 50% to 99% of recommended ACE inhibitor/ARB and beta-blocker doses results in comparable survival or heart failure–related hospitalization reduction (21), we considered patients successfully up-titrated when >50% of recommended dose was achieved after 3 months of up-titration.

The BIOSTAT-CHF population mainly consists of patients with advanced heart failure who may be more likely to have limited benefit from up-titration of ACE inhibitor/ARB and beta-blocker therapy. These patients may be worsened by even small doses of beta-blockers, or they may experience excessive hypotension and worsening renal function from ACE inhibitors/ARBs. BIOSTAT-CHF was specifically designed to record reasons for not up-titrating to recommended treatment doses. Only in 26% and 22% of the patients for ACE inhibitors/ARBs and beta-blockers, this was caused by intolerance to the drug because of organ dysfunction. In the majority of patients, no specific reason was provided (21). This analysis supports the concept that even less clinically ill patients may not be helped by ACE inhibitor/ARB and beta-blocker up-titration.

There were significant hemodynamic differences (heart rate and blood pressure) between patients who were up-titrated >50% of recommended treatment dose and those who were not. This might suggest that these and other variables were at least partly responsible for the different achieved up-titration doses. We corrected for these difference by propensity score matching and inverse probability of treatment weighing.

STUDY LIMITATIONS. One major important limitation of the present study is that heart failure treatment was not randomly assigned in our study. Up-titration of ACE inhibitors/ARBs and beta-blockers has been shown to be beneficial on average in many randomized clinical trials and has been adopted into the European Society of Cardiology heart failure guidelines. It is striking, however, that in clinical practice so many patients are not up-titrated to >50% of recommended dose. We tried to adjust for this treatment-indication bias, introduced in this cohort-type BIOSTAT-CHF study, by 2 generally accepted advanced statistical methods: propensity scoring and inverse probability of treatment weighing. Whether this corrected the treatment indication bias sufficiently is unfortunately not testable.

A second limitation is the large number of biomarkers that we analyzed, which increased the chance of false positive findings. We used Bonferroni correction of p values and we used sparse regression models to minimize the risk of overfitting. Lasso penalization is known to yield too large regression models (with too many predictor variables) (38), so our models might still be somewhat larger than necessary (on average >23 biomarkers). We used a repeated split-sample technique to cross-validate benefit and fit statistics to reduce the effect of overfitting.

A third limitation of our analyses was that we ignored patients who died in the first 3 months of the up-titration period. We excluded 151 deaths and the survival at 3 months was only 93%. We made a prediction model for the risk of death within 3 months and found that fibroblast growth factor 23, NT-proBNP, BNP, low hemoglobin, troponin I, ET1, ST2, WAP-4C, and C-reactive protein were the most important predictors of death within 3 months. This selection of biomarkers coincided largely with the set of biomarkers that we identified as prognostic in the patients who were not successfully up-titrated for both ACE inhibitors/ARBs and beta-blockers. Therefore, we assume that the presented results were not largely biased by the removal of the 151 deaths. We only had MRA dose data available after 9 months follow-up. This introduces additional bias because excluded even more patients than for the ACE inhibitor/ARB and

beta-blocker analyses. We tried to correct for this by inverse probability weighting. Although we cannot test if this was sufficient, we think the MRA data add important information to our models.

Because not all biomarkers used in our treatment selection models were measured in the validation cohort of the BIOSTAT-CHF study of 1,728 patients, we unfortunately could not validate our results in this cohort. In the future, and when funding is available we aim to measure the missing biomarkers and validate our treatment selection models in this cohort as well.

We found substantial differences between patients of which the model assumed not to benefit from ACE inhibitor/ARB up-titration and patients of which the model assumed not to benefit from beta-blocker up-titration. Patients not benefitting from ACE inhibitor/ARB up-titration were younger, with lower BNP and NT-proBNP, and higher hemoglobin levels. Patients not benefitting from beta-blocker up-titration, conversely, were more often older, had higher BNP and NT-proBNP, and had lower hemoglobin compared with patients benefitting from beta-blocker up-titration. BUN was elevated and heart rate was lower in both patients not benefitting from ACE inhibitor/ARB up-titration and patients not benefitting from beta-blocker up-titration.

Other possible limitations that could not be addressed in our cohort are the fact that our data are unfortunately limited to Caucasian patients only, and that there was a very low use of device therapy. This would possibly limit the use of our biomarker selection model in a more heterogeneous population. The percentage of device therapy is nevertheless comparable to the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) study, which recruited patients at the same time as BIOSTAT-CHF (39).

Biomarkers predictive for mortality or hospitalization were also markedly different between patients who were successfully up-titrated or not. This might have been expected because biomarkers related to ACE inhibition or ARB and beta-blocking pathways are likely to change substantially as a result of up-titration (40).

CONCLUSIONS

A biomarker-based treatment up-titration choice in patients with heart failure was favorable over both a hypothetical scenario in which all patients would have been successfully up-titrated to >50% of recommended of ACE inhibitor/ARB and beta-blocker dose and ≥50% MRA dose. We estimated that 1 in 50, 1 in 3, and 1 in 8 patients would not benefit from up-titration with ACE inhibitor/ARB, beta-blocker, or MRA, but their mortality or hospitalization hazards do not increase much by up-titration. Because of the nature of this study, and the small differences between biomarker-based treatment choice and the scenario in which all patients would have been successfully up-titrated, we suggest that up-titration should always be attempted in heart failure patients, which should lead to improved treatment of life-saving therapies across Europe.

ADDRESS FOR CORRESPONDENCE: Dr. Wouter Ouwerkerk, Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, Postbus 22660, room J1B-207, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: w.ouwerkerk@amc.uva.nl.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Not all patients with heart failure benefit from up-titrating treatment doses of recommended neurohormonal inhibitor medication. Predicting benefit based on individual biomarker profiles results in greater reduction of mortality and/or heart-failure-related hospitalization, although the difference is small.

TRANSLATIONAL OUTLOOK: Randomized trials comparing various models for selection of biomarker-guided treatment may provide insight into the pathogenesis of heart failure and expand treatment options

REFERENCES

1. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.

2. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450–6.

3. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349–55.

4. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.

5. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL

Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA 2000;283:1295–302.

6. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.

7. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.

8. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005;26:215–25.

9. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur Heart J 2008;29:2388–442.

10. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. Eur J Heart Fail 2012;14:803–69.

11. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution. Eur J Heart Fail 2016;18:891–975.

12. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709–17.

13. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More "malignant" than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 2001;3:315–22.

14. Jhund PS, Macintyre K, Simpson CR, et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation 2009;119:515–23.

15. Stewart S, Ekman I, Ekman T, Odén A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes 2010;3:573–80.

16. Voors AA, Ouwerkerk W, Zannad F, et al. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. Eur J Heart Fail 2017;2:429–36.

17. Cleland JGF. Contemporary management of heart failure in clinical practice. Heart 2002;88 Suppl 2:ii5–8.

18. Komajda M, Follath F, Swedberg K, et al. The EuroHeart Failure Survey programme–a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003;24:464–74.

19. Kalra PR, Morley C, Barnes S, et al. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. Int J Cardiol 2013;167:2695–9.

20. Voors AA, Anker SD, Cleland JG, et al. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. Eur J Heart Fail 2016;18:716–26.

21. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE inhibitors and beta-blockers in patients with heart failure: a prospective European study. Eur Heart J 2017;38:1883–90.

22. Apple FS, Christenson RH, Valdes R, et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. Clin Chem 1999;45:199–205.

23. Straface AL, Myers JH, Kirchick HJ, Blick KE. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. Am J Clin Pathol 2008;129:788–95.

24. Buuren S van, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67.

25. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515.

26. Liu LCY, Voors AA, Valente MAE, van der Meer P. A novel approach to drug development in heart failure: toward personalized medicine. Can J Cardiol 2014;30:288–95.

27. Schuetz P, Aujesky D, Müller C, Müller B. Biomarker-guided personalised emergency medicine for all - hope for another hype? Swiss Med Wkly 2015;145:w14079.

28. Demissei BG, Postmus D, Liu LCY, et al. Risk-based evaluation of efficacy of rolofylline in patients hospitalized with acute heart failure - Post-hoc analysis of the PROTECT trial. Int J Cardiol 2016;223:967–75.

29. Ouwerkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models for predicting mortality and/or heart failure hospitalization in patients with heart failure. J Am Coll Cardiol HF 2014;2:429–36.

30. Iqbal N, Wentworth B, Choudhary R, et al. Cardiac biomarkers: new tools for heart failure management. Cardiovasc Diagn Ther 2012;2:147–64.

31. Cauthen C a, Lipinski MJ, Abbate A, et al. Relation of blood urea nitrogen to long-term mortality in patients with heart failure. Am J Cardiol 2008;101:1643–7.

32. Shah KS, Maisel AS. Novel biomarkers in heart failure with preserved ejection fraction. Heart Fail Clin 2014;10:471–9.

33. Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. Circ Heart Fail 2008;1:2–5.

34. Toth PP. High-density lipoprotein and cardiovascular risk. Circulation 2004;109:1809–12.

35. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am Coll Cardiol 2002;39:1780–6.

36. van Deursen VM, Damman K, Voors AA, et al. Prognostic value of plasma neutrophil gelatinase-associated lipocalin for mortality in patients with heart failure. Circ Heart Fail 2014;7:35–42.

37. de Boer RA, Cao Q, Postmus D, et al. The WAP four-disulfide core domain protein HE4: a novel biomarker for heart failure. J Am Coll Cardiol HF 2013;1:164–9.

38. Musoro JZ, Zwinderman AH, Puhan MA, ter Riet G, Geskus RB. Validation of prediction models based on lasso regression with multiply imputed data. BMC Med Res Methodol 2014;14:116.

39. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.

40. van Veldhuisen DJ, Genth-Zotz S, Brouwer J, et al. High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. J Am Coll Cardiol 1998;32:1811–8.

KEY WORDS ACE inhibitor/ARB, beta-blocker, biomarkers, MRA, treatment decision

APPENDIX For an expanded Results section as well as supplemental tables and figures, please see the online version of this article.